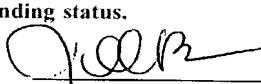


Mailed: 22 January 2002

I JC03 Rec'd PCT/PTO 22 JAN 2002

FORM PTO-1390 (REV. 12-2001)		U.S. DEPARTMENT OF COMMERCE PATENT AND TRADEMARK OFFICE	ATTORNEY'S DOCKET NUMBER
TRANSMITTAL LETTER TO THE UNITED STATES DESIGNATED/ELECTED OFFICE (DO/EO/US) CONCERNING A FILING UNDER 35 U.S.C. 371		3051-29752	
INTERNATIONAL APPLICATION NO.		INTERNATIONAL FILING DATE	U.S. APPLICATION NO. (If known, see 37 CFR 1.5 Unknown 10/031827
PCT/US00/40588		07 August 2000	PRIORITY DATE CLAIMED
09 August 1999			
TITLE OF INVENTION <b>ANTIVIRAL THERAPY USE OF P-GLYCOPROTEIN MODULATORS</b>			
APPLICANT(S) FOR DO/EO/US <b>WOOD, Alastair J. J.; KIM, Richard B.; WILKINSON, Grant R.</b>			
Applicant herewith submits to the United States Designated/Elected Office (DO/EO/US) the following items and other information:			
<p>1. <input checked="" type="checkbox"/> This is a <b>FIRST</b> submission of items concerning a filing under 35 U.S.C. 371.</p> <p>2. <input type="checkbox"/> This is a <b>SECOND</b> or <b>SUBSEQUENT</b> submission of items concerning a filing under 35 U.S.C. 371.</p> <p>3. <input type="checkbox"/> This is an express request to begin national examination procedures (35 U.S.C. 371(f)). The submission must include items (5), (6), (9) and (21) indicated below.</p> <p>4. <input checked="" type="checkbox"/> The US has been elected by the expiration of 19 months from the priority date (Article 31).</p> <p>5. <input checked="" type="checkbox"/> A copy of the International Application as filed (35 U.S.C. 371(c)(2))</p> <ol style="list-style-type: none"> <li><input checked="" type="checkbox"/> is attached hereto (required only if not communicated by the International Bureau).</li> <li><input type="checkbox"/> has been communicated by the International Bureau.</li> <li><input checked="" type="checkbox"/> is not required, as the application was filed in the United States Receiving Office (RO/US).</li> </ol> <p>6. <input type="checkbox"/> An English language translation of the International Application as filed (35 U.S.C. 371(c)(2)).</p> <ol style="list-style-type: none"> <li><input type="checkbox"/> is attached hereto.</li> <li><input type="checkbox"/> has been previously submitted under 35 U.S.C. 154(d)(4).</li> </ol> <p>7. <input checked="" type="checkbox"/> Amendments to the claims of the International Application under PCT Article 19 (35 U.S.C. 371(c)(3))</p> <ol style="list-style-type: none"> <li><input type="checkbox"/> are attached hereto (required only if not communicated by the International Bureau).</li> <li><input type="checkbox"/> have been communicated by the International Bureau.</li> <li><input type="checkbox"/> have not been made; however, the time limit for making such amendments has NOT expired.</li> <li><input checked="" type="checkbox"/> have not been made and will not be made.</li> </ol> <p>8. <input type="checkbox"/> An English language translation of the amendments to the claims under PCT Article 19 (35 U.S.C. 371(c)(3)).</p> <p>9. <input checked="" type="checkbox"/> An oath or declaration of the inventor(s) (35 U.S.C. 371(c)(4)). <b>(2 sheets)</b></p> <p>10. <input type="checkbox"/> An English language translation of the annexes of the International Preliminary Examination Report under PCT Article 36 (35 U.S.C. 371(c)(5)).</p>			
Items 11 to 20 below concern document(s) or information included:			
<p>11. <input checked="" type="checkbox"/> An Information Disclosure Statement under 37 CFR 1.97 and 1.98, <b>Form PTO 1449, and Copies of each reference cited therein</b></p> <p>12. <input type="checkbox"/> An assignment document for recording. A separate cover sheet in compliance with 37 CFR 3.28 and 3.31 is included.</p> <p>13. <input checked="" type="checkbox"/> A <b>FIRST</b> preliminary amendment.</p> <p>14. <input type="checkbox"/> A <b>SECOND</b> or <b>SUBSEQUENT</b> preliminary amendment.</p> <p>15. <input type="checkbox"/> A substitute specification.</p> <p>16. <input type="checkbox"/> A change of power of attorney and/or address letter.</p> <p>17. <input type="checkbox"/> A computer-readable form of the sequence listing in accordance with PCT Rule 13ter.2 and 35 U.S.C. 1.821 - 1.825.</p> <p>18. <input type="checkbox"/> A second copy of the published international application under 35 U.S.C. 154(d)(4).</p> <p>19. <input type="checkbox"/> A second copy of the English language translation of the international application under 35 U.S.C. 154(d)(4).</p> <p>20. <input checked="" type="checkbox"/> Other items or information:</p> <ol style="list-style-type: none"> <li><b>Copies of PCT International Search Report and Each Reference Cited Therein</b></li> <li><b>Copy of PCT Written Opinion</b></li> </ol>			

531 Rec'd PGI/PK 22 JAN 2002

U.S. APPLICATION NO. (if known, see 37 CFR 1.5)	INTERNATIONAL APPLICATION NO	ATTORNEY'S DOCKET NUMBER			
<b>Unknown US1827PCT/US00/40588</b>		<b>3051-69752</b>			
21. <input checked="" type="checkbox"/> The following fees are submitted:		CALCULATIONS PTO USE ONLY			
<b>BASIC NATIONAL FEE (37 CFR 1.492 (a) (1) - (5)):</b>					
Neither international preliminary examination fee (37 CFR 1.482) nor international search fee (37 CFR 1.445(a)(2)) paid to USPTO and International Search Report not prepared by the EPO or JPO. . . . .		\$1040.00			
International preliminary examination fee (37 CFR 1.482) not paid to USPTO but International Search Report prepared by the EPO or JPO . . . . .		\$890.00			
International preliminary examination fee (37 CFR 1.482) not paid to USPTO but international search fee (37 CFR 1.445(a)(2)) paid to USPTO . . . . .		\$740.00			
International preliminary examination fee (37 CFR 1.482) paid to USPTO but all claims did not satisfy provisions of PCT Article 33(1)-(4) . . . . .		\$710.00			
International preliminary examination fee (37 CFR 1.482) paid to USPTO and all claims satisfied provisions of PCT Article 33(1)-(4) . . . . .		\$100.00			
<b>ENTER APPROPRIATE BASIC FEE AMOUNT =</b>		<b>\$ 100.00</b>			
Surcharge of <b>\$130.00</b> for furnishing the oath or declaration later than <input type="checkbox"/> 20 <input type="checkbox"/> 30 months from the earliest claimed priority date (37 CFR 1.492(c)).		\$ -0-			
CLAIMS	NUMBER FILED	NUMBER EXTRA	RATE	\$	
Total claims	<b>22</b>	- 20 -	<b>2</b>	x \$18.00	<b>\$ 36.00</b>
Independent claims	<b>3</b>	- 3 -	<b>-0-</b>	x \$84.00	\$ -0-
MULTIPLE DEPENDENT CLAIM(S) (if applicable)			+ \$280.00	\$ -0-	
<b>TOTAL OF ABOVE CALCULATIONS =</b>		<b>\$ 136.00</b>			
<input type="checkbox"/> Applicant claims small entity status. See 37 CFR 1.27. The fees indicated above are reduced by 1/2.		\$ -0-			
<b>SUBTOTAL =</b>		<b>\$ 136.00</b>			
Processing fee of <b>\$130.00</b> for furnishing the English translation later than <input type="checkbox"/> 20 <input type="checkbox"/> 30 months from the earliest claimed priority date (37 CFR 1.492(f)).		\$ -0-			
<b>TOTAL NATIONAL FEE =</b>		<b>\$ 136.00</b>			
Fee for recording the enclosed assignment (37 CFR 1.21(h)). The assignment must be accompanied by an appropriate cover sheet (37 CFR 3.28, 3.31). \$40.00 per property +		\$ -0-			
<b>TOTAL FEES ENCLOSED =</b>		<b>\$ 136.00</b>			
		Amount to be refunded:	\$		
		charged:	\$		
<p>a. <input checked="" type="checkbox"/> A check in the amount of <b>\$ 136.00</b> to cover the above fees is enclosed</p> <p>b. <input type="checkbox"/> Please charge my Deposit Account No. _____ in the amount of \$ _____ to cover the above fees. A duplicate copy of this sheet is enclosed.</p> <p>c. <input checked="" type="checkbox"/> The Commissioner is hereby authorized to charge any additional fees which may be required, or credit any overpayment to Deposit Account No. <b>10-0435</b>. A duplicate copy of this sheet is enclosed.</p> <p>d. <input type="checkbox"/> Fees are to be charged to a credit card. <b>WARNING:</b> Information on this form may become public. <b>Credit card information should not be included on this form.</b> Provide credit card information and authorization on PTO-2038.</p>					
<p><b>NOTE: Where an appropriate time limit under 37 CFR 1.494 or 1.495 has not been met, a petition to revive (37 CFR 1.137 (a) or (b)) must be filed and granted to restore the application to pending status.</b></p>					
SEND ALL CORRESPONDENCE TO					
<b>LAMMERT, Steven R. BARNES &amp; THORNBURG 11 South Meridian Street Indianapolis, IN 46204 US</b>					
 <b>Jill T. POWLICK</b> NAME <b>42088</b> REGISTRATION NUMBER					

BARNES & THORNBURG

10/031827  
531 Rec'd PCT/P. 22 JAN 2002

11 South Meridian Street  
Indianapolis, Indiana 46204  
(317) 236-1313

PATENT APPLICATION

*IN THE UNITED STATES PATENT AND TRADEMARK OFFICE*

*Group:* Unknown

Certificate Under 37 CFR 1.10

*Attorney*

Express Mail Label No. EL230048285US

*Docket:* 3051-69752

Date of Deposit 22 January 2002

*Applicant:* WOOD, Alastair J. J.; KIM, Richard B.;  
WILKINSON, Grant R.

I hereby certify that this paper or fee is being deposited with the United States Postal Service's "Express Mail Post Office to Addressee" service under 37 CFR 1.10 on the date indicated above and is addressed to: Commissioner for Patents, Washington, D.C. 20231

*Invention:* ANTIVIRAL THERAPY USE OF P-GLYCOPROTEIN MODULATORS

Mary Jean Eskridge  
Typed or Printed Name of Person Mailing Paper or Fee

*U.S. Serial No.:* Unknown

Mary Jean Eskridge  
Signature of Person Mailing Paper or Fee

*International Serial No.:* PCT/US00/40588

*International Filing Date:* 07 August 2000  
(07.08.00)

*Earliest Priority Date:* 09 August 1999  
(09.08.99)

FIRST PRELIMINARY AMENDMENT

Attention: DO/EO/US  
Box PCT  
Commissioner for Patents  
Washington, D.C. 20231

Sir:

Preliminary to the examination of the above-identified national patent application submitted herewith, applicants request entry of the following amendments.

Abstract

Please enter the Abstract of the Disclosure submitted as a separate paper.

Drawings

Please enter the drawings attached hereto submitted as separate papers.

In the Description

After the title, please insert the following paragraph:

Cross-References to Related Applications

This application is a U.S. national counterpart application of international application serial No. PCT/US00/40588 filed August 7, 2000, which claims priority to U.S. application serial no. 09/370,266 filed August 9, 1999.

In the Claims

Please delete claims 23-36 without prejudice.

REMARKS

This Preliminary Amendment is being submitted to indicate the relationship of the subject U.S. national application to previously filed applications as required under 37 C.F.R. 1.78.

No amendment is believed to go beyond the disclosure in the international application as originally filed.

With the entry of the foregoing amendments, the application is believed to be in condition for examination and allowance. Consideration of the claims, leading to their allowance and passage of the application to issuance, is respectfully requested.

Respectfully submitted,



Jill T. Powlick  
Atty. Reg. No. 42088  
Attorney for Applicants

JTP/mje/424872  
Indianapolis, Indiana 46204  
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10/031827  
531 Rec'd PCT/R. 22 JAN 2002

Abstract of the Disclosure

The present invention relates to a pharmaceutical composition comprising a 10, 11 methanodibenzosuberane and use thereof for the treatment of HIV infection. Co-administration of the 10, 11 methanodibenzosuberane with an HIV protease inhibitor increases the concentration of the protease inhibitor in certain tissues, including the brain and testes, without substantially increasing plasma levels of the protease inhibitor. Accordingly, additional antiviral therapy can be achieved without use of increased drug dosages, thereby reducing the potential for occurrence of undesirable side effects deriving from drug toxicity.

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531 Rec'd PCT/NP 22 JAN 2002

Cross-References to Related Applications

This application is a U.S. national counterpart application of international application serial No. PCT/US00/40588 filed August 7, 2000, which claims priority to U.S. application serial no. 09/370,266 filed August 9, 1999.

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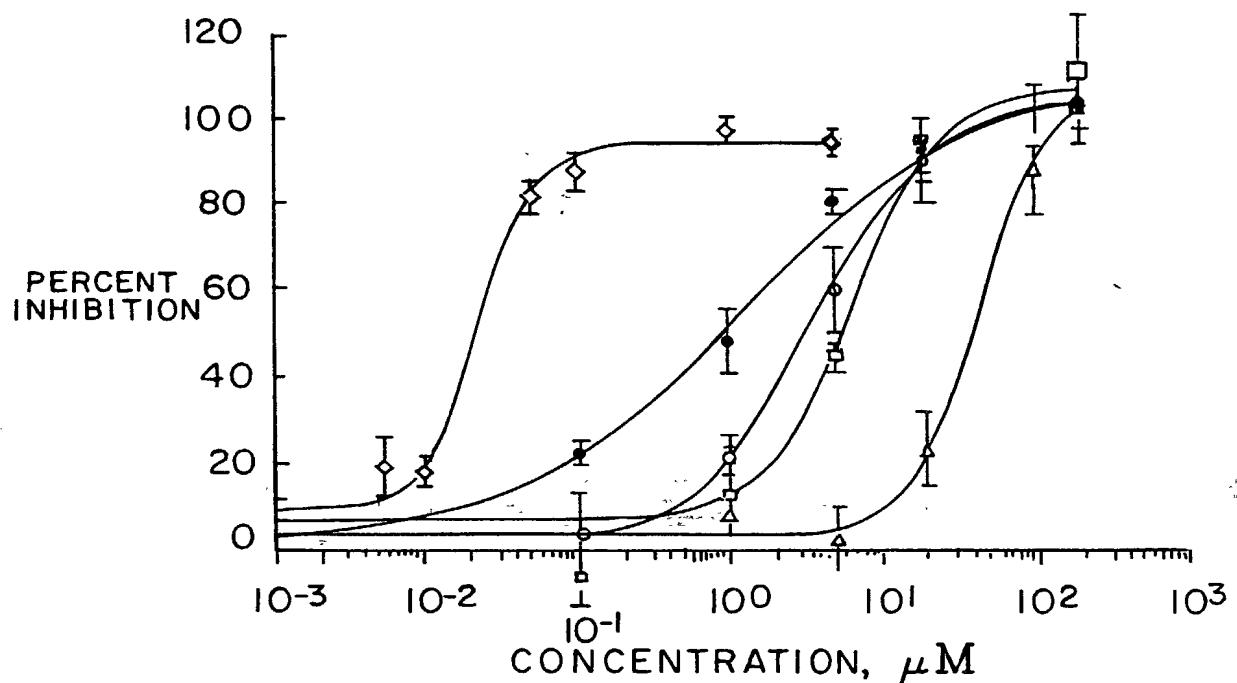


FIG. 1

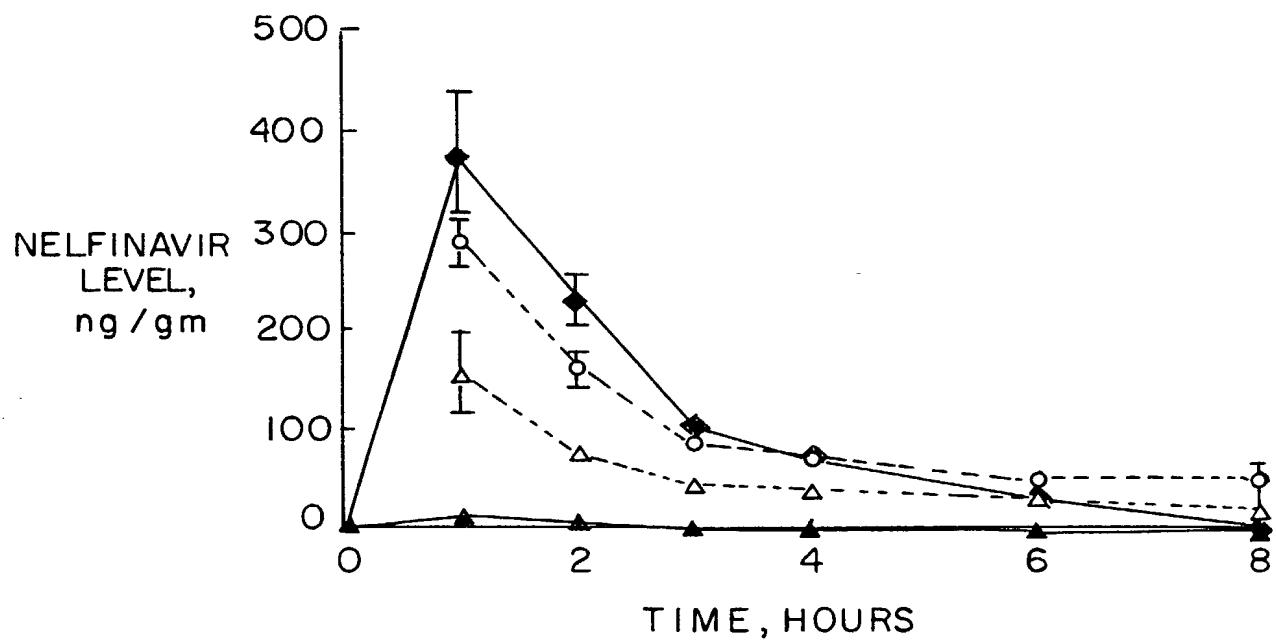
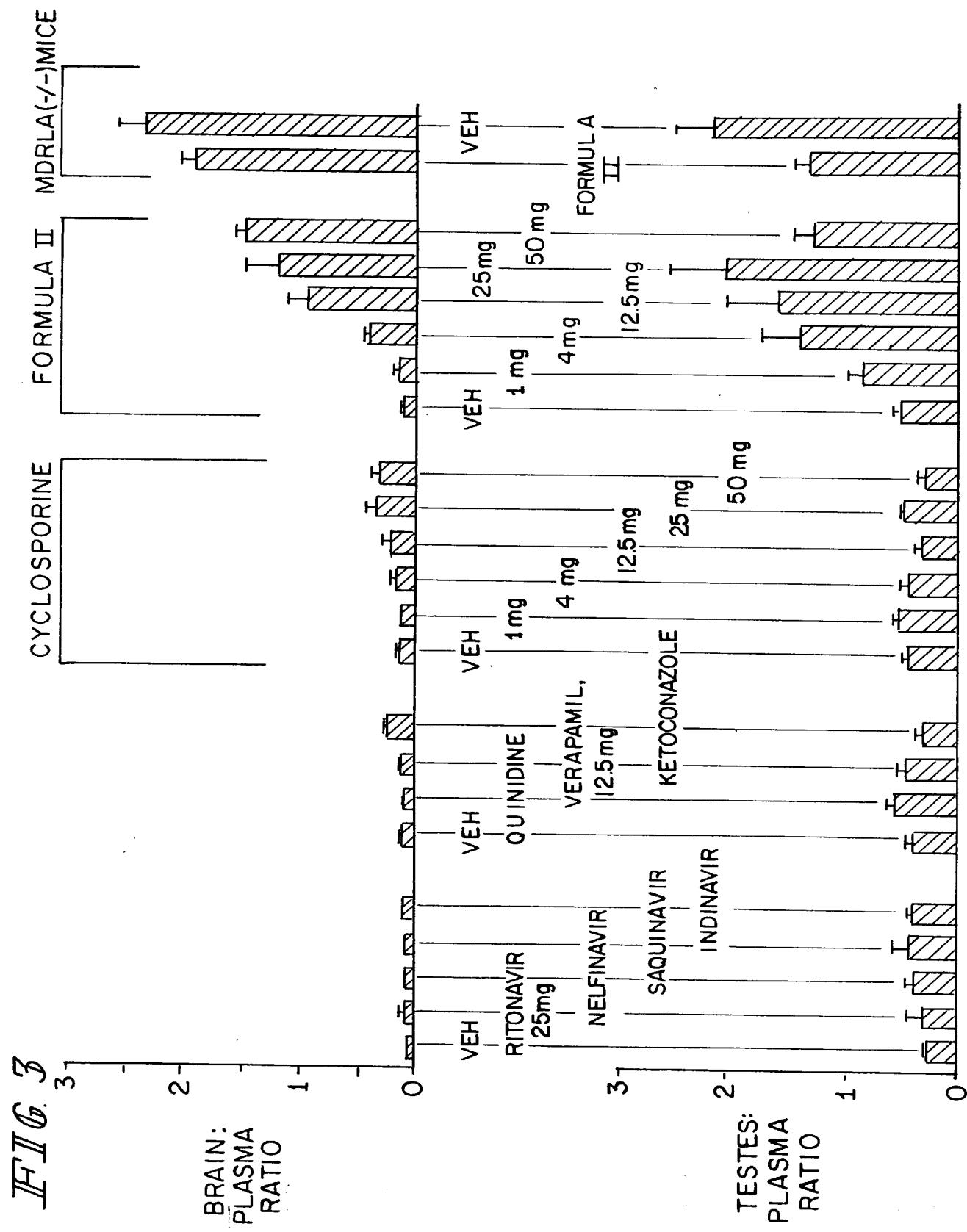


FIG. 2

3 100 3 1002 107031827



ANTIVIRAL THERAPY USE OF P-GLYCOPROTEIN MODULATORSField of the Invention

The present invention relates to treatment of viral infections. More particularly the present invention is directed to the use of certain P-glycoprotein modulators to increase the concentration of HIV-protease inhibitors in certain tissues.

Background and Summary of the Invention

HIV protease inhibitors have proven to be effective in the treatment of 10 HIV-1 infection. However, the utility of such drugs can be limited due to poor transport across certain biological membranes. Oral absorption of protease inhibitors is often low and variable, and penetration into certain tissues, including the brain and testes, is often poor. The resultant non-uniform distribution of the antiviral drug in the body leaves certain tissues as sanctuaries for viral proliferation.

15 P-glycoprotein is an ATP dependent efflux membrane transporter with broad substrate specificity for a variety of structurally diverse drugs. P-glycoprotein is distributed in various normal tissues, including, of particular importance in drug disposition, epithelial cells in the gastrointestinal tract, the liver, and the kidney. Apical expression of P-glycoprotein in such tissues results in reduced absorption 20 (gastrointestinal tract), and enhanced elimination into the bile (liver) and urine (kidney) for drugs functioning as P-glycoprotein substrates. In addition, expression of P-glycoprotein at the level of the blood-brain barrier has been shown to be a critical factor in preventing the entry of some drugs into the central nervous system. Previous work has shown that various HIV-1 protease inhibitors are substrates of P-glycoprotein, explaining some of the limits on membrane permeability of these drugs. See, for example, Kim, R.B., et al., The Drug Transporter P-Glycoprotein Limits Oral 25 Absorption and Brain Entry of HIV-1 Protease Inhibitors, J. Clin. Invest., 101:289-294, 1998.

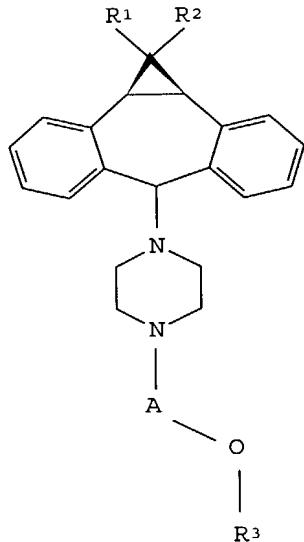
Certain 10,11-methanodibenzosuberane derivatives have been shown 30 to be pharmaceutically active agents in the treatment of multidrug resistance in cancer therapy. See, for example, U.S. Patents Nos. 5,654,304 and 5,874,434. Such compounds are known to interact with P-glycoprotein.

The present invention relates to a use of a 10,11-methanodibenzosuberanes of formula (I):

5

10

I



15 wherein: A is -CH<sub>2</sub>CH<sub>2</sub>-; -CH<sub>2</sub>CHR<sup>a</sup>CH<sub>2</sub>- where R<sup>a</sup> is H, OH or lower acyloxy; or -CH<sub>2</sub>CHR<sup>b</sup>CHR<sup>c</sup>CH<sub>2</sub>- where one of R<sup>b</sup> or R<sup>c</sup> is H, OH, or lower acyloxy, and the other is H;

R<sup>1</sup> is H, F, Cl, or Br;

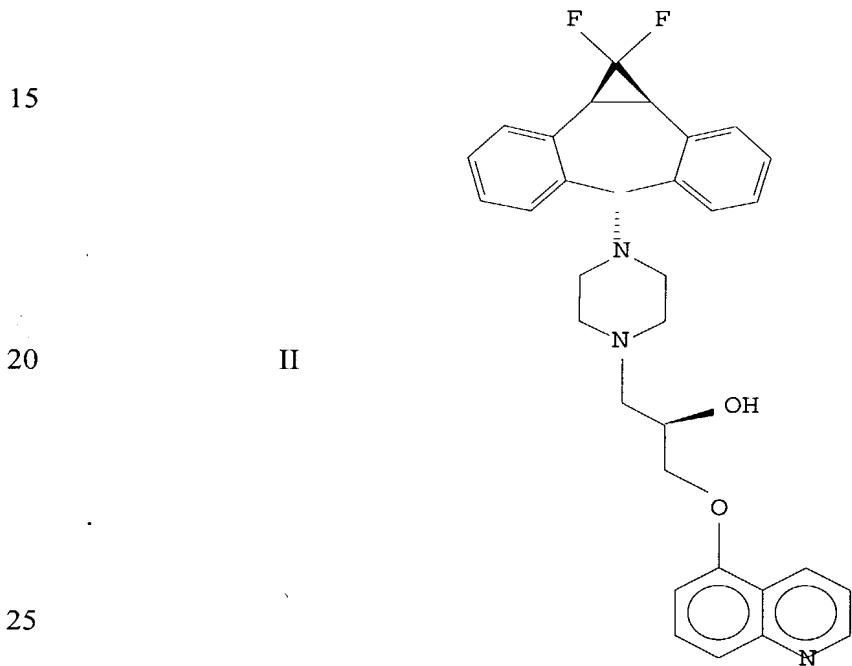
R<sup>2</sup> is H, F, Cl, or Br; and

20 R<sup>3</sup> is heteroaryl or phenyl optionally substituted with F, Cl, Br, CF<sub>3</sub>, CN, NO<sub>2</sub>, or OCHF<sub>2</sub>; or a pharmaceutically acceptable salt thereof; for the manufacture of a medicament for the treatment of HIV in a patient undergoing treatment with an HIV protease inhibitor. The use increases the concentration of the HIV inhibitor in the brain and/or testes of the patient without significantly increasing plasma levels of the protease inhibitor. Accordingly, more effective antiviral therapy can be achieved without use of increased drug dosages, thereby reducing the potential for occurrence of undesirable side effects deriving from drug toxicity. Thus, one aspect of this invention relates to a method for increasing the concentration of an HIV protease inhibitor in the brain of a patient, the method comprising administering to an HIV infected patient an amount of a 10,11-methanodibenzosuberane of formula (I), or a pharmaceutically acceptable salt thereof, and co-administering to the patient a therapeutically effective amount of the protease inhibitor.

Another related aspect of this invention is a method of treatment of an HIV infected patient. The method comprises administering a compound comprising a 10,11-methanodibenzosuberane of formula (I) in an amount effective to increase the concentration of a co-administered protease inhibitor in the brain and testes of the patient.

In another embodiment, the 10,11-methanodibenzosuberane of formula (I) is administered in combination with a protease inhibitor to increase concentrations of the protease inhibitor in the brain.

Still another aspect of this invention is a pharmaceutical composition comprising a protease inhibitor, most preferably nelfinavir, and a 10,11-methanodibenzosuberane of formula (I), with a pharmaceutical carrier. In a preferred embodiment, the 10,11-methanodibenzosuberane is a compound of formula (II):



Still another aspect of this invention is the use of an HIV protease inhibitor for the manufacture of a medicament for the treatment of HIV wherein the concentration of the protease inhibitor in the brain is increased by co-administration with a 10,11-methanodibenzosuberane of formula (I), or a pharmaceutically acceptable salt thereof.

- (i) preventing the disease, that is, causing the clinical symptoms of the disease not to develop;
- (ii) inhibiting the disease, that is, arresting the development of clinical symptoms; and/or
- 5 (iii) relieving the disease, that is, causing the regression of clinical symptoms.

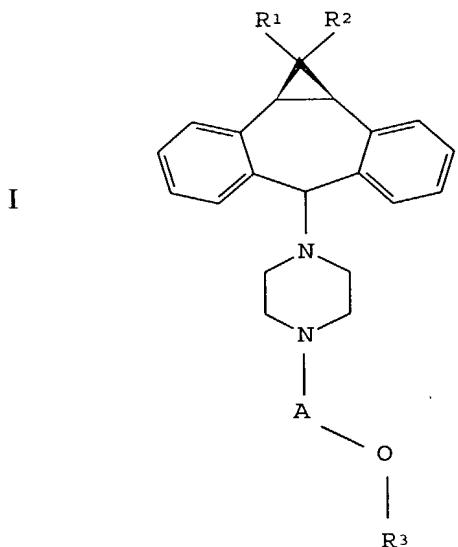
The term "effective amount" means a dosage sufficient to provide treatment for the disease state being treated. This will vary depending on the patient, the disease and the treatment being effected.

10 The term "co-administer" means the administration of more than one active agent as part of the same treatment regimen, whether they are administered simultaneously or at different times.

"Structure of formula (I)" refers to the generic structure of the compounds of the invention.

15 The present invention is a method for increasing the concentration of an HIV protease inhibitor in the brain and testes of a patient, said method comprising administering to an HIV-infected patient an amount of a 10,11-methanodibenzosuberanes of the formula (I):

20



25

30

wherein: A is -CH<sub>2</sub>CH<sub>2</sub>-; -CH<sub>2</sub>CHR<sup>a</sup>CH<sub>2</sub>- where R<sup>a</sup> is H, OH or lower acyloxy; or -CH<sub>2</sub>CHR<sup>b</sup>CHR<sup>c</sup>CH<sub>2</sub>- where one of R<sup>b</sup> or R<sup>c</sup> is H, OH, or lower acyloxy, and the other is H;

R<sup>1</sup> is H, F, Cl, or Br;

5 R<sup>2</sup> is H, F, Cl, or Br; and

R<sup>3</sup> is heteroaryl or phenyl optionally substituted with F, Cl, Br, CF<sub>3</sub>, CN, NO<sub>2</sub>, or OCHF<sub>2</sub>; or a pharmaceutically acceptable salts thereof; and co-administering to the patient a therapeutically effective amount to the protease inhibitor.

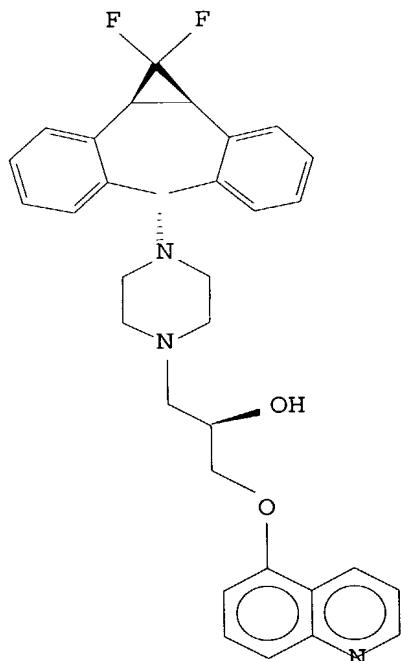
10 In a preferred embodiment, a compound of formula (I) is used wherein A is -CH<sub>2</sub>CHR<sup>a</sup>CH<sub>2</sub>-. In another preferred embodiment, R<sup>1</sup> and R<sup>2</sup> are F. In still another preferred embodiment, R<sup>3</sup> is an optionally substituted quinolyl, preferably quinol-5-yl.

15 In another preferred embodiment of the present invention, a compound of formula (II):

20

II

25



30 is employed with protease inhibitors in the method of the present invention.

Examples of such protease inhibitors contemplated by the present invention are NELFINAVIR, which is preferably administered as the mesylate salt at

750 mg three times per day (Agouron Pharmaceuticals (La Jolla, CA)) (U.S. Patent No. 5,484,926); RITONAVIR, which is preferably administered at 600 mg twice daily (Roche Ltd. (Lewes, UK) (U.S. Patent No. 5,484,801); SAQUINAVIR, which is preferably administered as the mesylate salt at 1,200 mg three times per day (Roche 5 Discovery (Rahway, NJ)) (U.S. Patent No. 5,196,438); INDINAVIR, which is preferably administered as the sulfate salt at 800 mg three times per day (Merck Research Laboratories) (U.S. Patent No. 5,413,999); and AMPRENAVIR, which is preferably administered at 1,200 mg twice daily (U.S. Patent No. 5,585,397). The skilled artisan would recognize that this list is not exhaustive. Additionally the skilled 10 artisan would recognize that the protease inhibitor's administration to a patient may vary from the preferred.

The HIV-1 virus enters the brain and other organs such as the testes relatively early after primary infection. Reduction of the viral load in such organs has proven to be difficult, as most of the current HIV antiviral agents do not readily 15 penetrate into the tissues to provide concentrations effective to prevent viral replication. See Groothius, D.R., and Levy, R.M., The entry of antiviral drugs into the central nervous system, *J. NeuroVirology*, 3:387-400, 1997. The low rate of drug transport into these pharmacologic sanctuary sites is the consequence of a functional barrier to drug entry. HIV protease inhibitors have been found to be excellent 20 substrates for the membrane efflux pump P-glycoprotein, which is localized in the apical domain of capillary endothelial cells of the brain and testis. The P-glycoprotein pump works to limit drug distribution into these tissues. See, for example, Kim, R.B., et al., The drug transporter P-glycoprotein limits oral absorption and brain entry of 25 HIV-1 protease inhibitors, *J. Clin. Invest.*, 101:289-294, 1998; Lee, C.G.L., et al., HIV-1 protease inhibitors are substrates for the *mdrl* multidrug transporter, *Biochemistry*, 37:3594-3601, 1998; Kim, A.E., et al., Saquinavir, an HIV protease inhibitor, is transported by P-glycoprotein, *J. Pharmac. Exp. Ther.*, 286:1439-1445, 1998; Thiebaut, F., et al., Cellular localization of the multidrug resistance gene product P-glycoprotein in normal human tissue, *Proc. Natl. Acad. Sci., U.S.A.*, 30 84:7735-7738, 1987; Gordon-Cardo, C., et al., Multidrug-resistance gene (P-glycoprotein) is expressed by endothelial cells at blood-brain barrier sites, *Proc. Natl. Acad. Sci., U.S.A.*, 86:695-698, 1989.

The present invention enables pharmacological inhibition of the functional activity of the P-glycoprotein transporter on HIV protease inhibitor substrates through use of a 10,11-methanodibenzosuberane of formula (I) co-administered with an HIV protease inhibitor. Such modulation of P-glycoprotein activity results in significantly enhanced HIV protease inhibitor concentrations in both the brain and testes relative to drug concentration in plasma.

The magnitude of the effect of P-glycoprotein inhibition attainable by administration of the compounds of formula (I) is tissue dependent; for example, the tissue:plasma drug concentration ratio is enhanced in the brain to a greater extent than in the testes. This difference is believed to be related to the level of P-glycoprotein function in the respective tissues. There is about a 30-fold difference in nelfinavir concentration in the brain of *mdrla(+/+)* and *mdrla(-/-)* mice compared to only a 4-fold concentration difference in the testes. P-glycoprotein inhibition using the compounds of formula (I) exhibits similar tissue differences. Notably, however, nelfinavir concentration differences achieved in both organs indicates a 75 to 90% absence of P-glycoprotein function based on comparable data in the *mdrla(-/-)* mice. At the highest doses of the compound of formula (II), the concentrations of nelfinavir in the brain and testes are equal to or higher than the drug concentration in plasma. Co-administration of a 10,11-methanodibenzosuberane of formula (I) with an HIV protease inhibitor in accordance with this invention minimizes P-glycoprotein modulated drug concentration differences between plasma and the brain and testes, thereby reducing or eliminating these tissues as sanctuaries for viral proliferation in patients receiving protease inhibitor therapy.

The present invention provides advantages over use of prior art P-glycoprotein inhibitors such as quinidine, verapamil, valspodar, and cyclosporine A, which are known to interact with drug metabolizing enzymes, in particular, members of the cytochrome P4503A subfamily (CYP3A). Inhibitors of P-glycoprotein are frequently inhibitors of CYP3A and vice-versa. See, for example, Wacher, V.J., et al., Overlapping substrate specificities and tissue distribution of cytochrome P4503A and P-glycoprotein: implications for drug delivery and activity in cancer chemotherapy, Mol. Carcinogen, 13:129-134, 1995; Kim, R.B., et al., Interrelationship between substrates and inhibitors of human CYP3A and P-

glycoprotein, Pharm. Res., 16:408-44, 1999. Accordingly, with drugs such as quinidine, verapamil, valsopdar, and cyclosporine A, a dual interaction occurs whereby reduced P-glycoprotein function is associated with increased plasma levels of the CYP3A substrate.

5           Although many P-glycoprotein inhibitors impair CYP3A-mediated metabolism, this is not an absolute relationship. In fact, the two characteristics appear to be independently determined such that some CYP3A inhibitors do not cause significant impairment of P-glycoprotein function and, more importantly, the reverse situation is possible, i.e., effective transporter inhibition with minimal effect on  
10          CYP3A. See Wandel, C., et al., P-glycoprotein and cytochrome P4503A inhibition: dissociation of inhibitory potencies, Cancer Res., in press, 1999. The 10,11-methanodibenzosuberanes of formula (I) are representative of such drugs. For example, the affinity of the compound of formula (II) for CYP3A is some 40-fold less than that for P-glycoprotein. Shepard, R.L., et al., Selectivity of the potent P-  
15          glycoprotein modulator, LY335979, Proc. Amer. Assoc. Cancer. Res., 39:362, 1998; Dantzig, A., J. Pharmco. Exp. Ther., 290:854-862, 1999. This selectivity would account for the relative small formula (II)-induced changes in nelfinavir's plasma level. Thus, the present invention has advantages over prior art P-glycoprotein inhibitors, since systemic toxicity from the antiviral agent would not be expected to  
20          increase following administration of compounds of formula (I).

An additional problem associated with prior art use of P-glycoprotein modulators has been their limited potency. Because of this limited potency, effective levels have been difficult to achieve without adverse effects. The minimal effects of quinidine, verapamil, ketoconazole, and cyclosporine A on nelfinavir's tissue:plasma ratios are consistent with such low potency as demonstrated by their  $IC_{50}$  values relative to digoxin translocation across Caco-2 cells. By contrast, the compound of formula (II), which is at least 50-fold more potent than the other inhibitors, produced 75% to 90% inhibition of P-glycoprotein transport in both the brain and testes. This finding emphasizes the importance of potency in the application of P-glycoprotein  
25          modulators.  
30

Another issue of selectivity by currently available P-glycoprotein modulators is related to the inhibition of P-glycoprotein itself versus other membrane

transporters that may also be involved in drug efflux or drug uptake into the cell. An increasing number of both types of membrane transporters have been identified and characterized in various cells/tissues within the body. Moreover, cross-inhibition of different transports appears to occur. For example, a number of P-glycoprotein inhibitors such as quinidine, verapamil, ketoconazole, and valspodar also impair drug uptake by OATP, but at higher concentrations than those required for inhibition of the efflux transporter. See Cvetkovic, M., et al., OATP and P-glycoprotein transporters mediate the coordinate cellular uptake and excretion of fexofenadine, *Drug Metab. Disp.*, 27:866-871, 1999. Because an OATP type of transporter is present in the brain, (see Noe, B., Isolation of a multispecific organic anion and cardiac glycoside transporter from rat brain, *Proc. Natl. Acad. Sci.*, 94:10346-10350, 1997), it is not unreasonable to suggest that the observed reduction in nelfinavir's plasma ratio with higher doses of cyclosporine A reflects such non-selectivity. A similar effort with valspodar has also been observed with another P-glycoprotein substrate - digoxin. In contrast, since the brain:plasma ratio continues to increase over the whole dose range studied, compound of formula (II) does not appear to inhibit transporters other than P-glycoprotein, at least in the brain. See Dantzig, *supra*.

Thus, the present invention employs the 10,11-methanodibenzosuberanes of formula (I) to increase HIV protease inhibitor concentrations in the brain and testes, without an associated increase in plasma concentrations.

The 10,11-methanodibenzosuberanes of formula (I) are typically co-administered with an HIV protease inhibitor, such as nelfinavir, saquinavir, indinavir, ritonavir, or amprenavir. In one preferred drug administration protocol a patient is pretreated with one or more doses of a compound of formula (I), and another dose of the P-glycoprotein inhibitor is administered concurrently with a dose of the HIV protease inhibitor. Typically, HIV protease inhibitors are administered orally in tablet form three times per day, in amounts of 600 to 1200 mg per dose. Administration of the compounds of formula (I) can be via any accepted mode of drug administration.

Dosage levels of the compound of formula (I) for use in accordance with this invention range can vary according to patient condition and weight but

generally range from about 0.01 to about 50 mg/kg of patient body weight, more preferably about 0.1 to 10 mg/kg of body weight, and most preferably about 0.3 to 2.0 mg/kg of body weight per dose.

The administration of the compounds of formula (I) in HIV treatment protocols with protease inhibitors in accordance with this invention can be carried out using any pharmaceutically acceptable mode of drug administration. The compounds of formula (I) can be administered either alone or more typically in combination with pharmaceutically acceptable excipients, including those used in formulating solid, semi-solid, liquid, or aerosol dosage forms, such as, for example, tablets, capsules, powders, liquids, suspensions, suppositories, nasal solutions, aerosols or the like. The compounds of formula (I) can also be administered in sustained or controlled release dosage forms, including depot injections, osmotic pumps, biodegradable matrices, transdermal (including electrotransport) patches, and the like, for the prolonged administration of the compound at a predetermined rate, preferably in unit dosage forms suitable for administration of precise dosages. The compositions will typically include a conventional pharmaceutical carrier or excipient and a compound of formula (I). In addition, the present compositions may include other medicinal agents, pharmaceutical agents, carriers, adjuvants, etc., including a suitable dose of an HIV protease inhibitor. Generally, depending on the intended mode of administration, the pharmaceutically acceptable composition will contain about 0.1% to 90%, preferably about 0.5% to 50%, by weight of a compound or salt of formula (I), the remainder being suitable pharmaceutical excipients, carriers, etc.

One manner of administration of the compounds of formula (I) is oral, using a convenient daily dosage regimen which can be adjusted according to patient condition and total antiviral treatment protocol. For oral administration, a pharmaceutically acceptable composition is formulated by the combination of a compound of formula (I) and optional protease inhibitor with any of the normally employed pharmaceutical excipients, for example, mannitol, lactose, starch, magnesium stearate, sodium saccharine, talcum, cellulose, sodium cross carmellose, glucose, gelatin, sucrose, magnesium carbonate, propylene carbonate, vegetable oils, or triglycerides, and the like. Such dosage compositions include solutions, suspensions, tablets, dispersible tablets, capsules, powders, lozenges, sustained release

formulations and the like. Preferably the compositions for oral administration will take the form of a tablet, capsule, or caplet.

Liquid pharmaceutical compositions in accordance with this invention can be prepared by dissolving, dispersing, etc. an active compound of formula (I) and optional pharmaceutical adjuvants in a carrier, such as, for example, water, saline, aqueous dextrose, glycerol, glycals, ethanol, and the like, to form a solution or suspension. If desired, the pharmaceutical composition to be administered may also contain minor amounts of nontoxic auxiliary substances such as wetting agents, emulsifying agents, or solubilizing agents, pH buffering agents and the like, for example, acetate, citrate, cyclodextrine derivatives, sorbitan monolaurate, triethanolamine sodium acetate, triethanolamine oleate, etc.

Dosage forms or compositions containing active ingredient in the range of 0.005% to 95% with the balance made up from non-toxic carrier may be prepared. Other useful formulations include those set forth in U.S. Pat. Nos. Re. 28,819 and 4,358,603.

The present invention can also be carried out using formulations for parenteral administration, i.e., subcutaneous, intramuscular, intrathecal, or intravenous administration. Injectable dosage forms of this invention can be prepared as liquid solutions or suspensions, solid forms suitable for dissolution or suspension in liquid prior to injection, or as emulsions. Suitable excipient carriers are, for example, water, saline, dextrose, glycerol, ethanol or the like. In addition, if desired, the pharmaceutical compositions to be administered may also contain minor amounts of non-toxic auxiliary substances such as wetting or emulsifying agents, pH buffering agents, solubility enhancers, and the like, such as for example, sodium acetate, sorbitan monolaurate, triethanolamine oleate, cyclodextrins, etc. A more recently devised approach for parenteral administration employs the implantation of a slow-release or sustained-release system, such that a more or less constant rate of drug release is maintained. See, e.g., U.S. Pat. No. 3,710,795.

The percentage of active compound contained in such parenteral compositions depends on the specific use and the needs of the subject. However, percentages of active ingredient of 0.01% to 10% in solution are acceptable, and they may be higher if the composition is a solid which will be subsequently diluted to the

above percentages. Preferably the composition will comprise 0.2 - 10% of the active agent in solution.

#### EXAMPLES

5           The following preparations and examples are given to enable those skilled in the art to more clearly understand and to practice the present invention. They should not be considered as limiting the scope of the invention, but merely as being illustrative and representative thereof.

10       Example 1

Inhibition of the P-glycoprotein transport pump was measured as a function of inhibition of digoxin transport in an *in vitro* culture system. Inhibition of digoxin transport was determined using a polarized monolayer of Caco-2 cells. Caco-2 cells were grown and cultured on 0.4 µm polycarbonate membrane filters as described in Kim, R.B., et al., The drug transporter P-glycoprotein limits oral absorption and brain entry of HIV-1 protease inhibitors, *J. Clin. Invest.*, 101:289-294, 1998. Transport of [<sup>3</sup>H]-digoxin (15 Ci/mmol; Dupont-New England Nuclear, Boston, MA) was determined by its addition to either the basal or apical side of the polarized cell monolayer, and the transport over a four hour period of time of 15 radioactivity into the other compartment was measured in the absence or presence of putative inhibitor in both compartments. The extent of inhibition by each putative inhibitor was determined using the following equation:

20           
$$\text{% inhibition} = 1 - \left[ \frac{i_{B-A} - i_{A-B}}{\alpha_{B-A} - \alpha_{A-B}} \right] \times 100$$

25           where  $i$  and  $\alpha$  are the percentages of digoxin transport in the presence and absence of inhibitor, according to the direction of transport. IC<sub>50</sub> values were estimated from the Hill equation using the computer program Prism® (GraphPad Software Inc., San Diego, CA), and the data represent results obtained from at least 3 preparations on different days.

-14-

IC<sub>50</sub> values were calculated for various known P-glycoprotein inhibitors; ketoconazole (1.2 μM), cyclosporine A (1.3 μM), verapamil (2.1 μM) and quinidine (2.2 μM), were in the low micromolar range. Fig. 1 illustrates the P-glycoprotein inhibition observed with various other putative inhibitors. Nelfinavir exhibited comparable 5 inhibitory potency (1.4 μM) to the potency of the known P-glycoprotein inhibitors. However, ritonavir (3.8 μM) and saquinavir (6.5 μM) were somewhat less potent, and the IC<sub>50</sub> value for indinavir (44μM) was about an order of magnitude greater than the IC<sub>50</sub> values for the other HIV protease inhibitors. As shown in Fig. 1, the compound 10 of formula (II) was by far the most potent of the P-glycoprotein inhibitors studied, with an IC<sub>50</sub> value (0.024 μM) over 50-fold lower than cyclosporine A.

Example 2

The tissue distribution of nelfinavir in the absence of any other putative inhibitor was determined in *mdrla*(++) and *mdrla*(-/-) mice. Male *mdrla*(-/-) 15 mice (FVB/TacfBR-[KO]mdrlaN7), 6-12 weeks of age and genetically matched male *mdrla*(++) mice (FVB/MTtacfBR) weighing 20 to 30 g were obtained from Taconic (Germantown, NY). The animals were cared for in accordance with the USPHS policy for the Care and Use of Laboratory Animals and the experimental studies were approved by the Vanderbilt University Animal Care Committee.

20 The tissue distribution of [<sup>14</sup>C]-nelfinavir (8.5 mCi/mmol, Agouron Pharmaceuticals, Inc., San Diego, CA) was determined following intravenous injection (5 mg/kg) of an ethanol/0.9% saline solution over 5 minutes into a tail vein; the total volume injected was 4 μl/g. At specific times after drug administration and following anesthesia with isoflurane (Isoflo, Abbott Laboratories, Abbott Park, IL), 25 blood was removed by orbital bleeding and the animal sacrificed. Subsequently, tissues were harvested, weighed, and homogenized with 4% bovine serum albumin solution. Total radioactivity was determined after the addition of 100 μl plasma or 500 μl tissue homogenate to vials containing 4 ml scintillation fluid (Scintiverse BD\*, Fisher Scientific Co., Fairlawn, NJ). The brain:plasma ratio was 0.06 in the 30 *mdrla*(++) mice, whereas the brain:plasma ratio was 2.3 in the *mdrla*(-/-) mice. The distribution also varied in the testes, where the *mdrla*(++) mice had a 0.29 testes:plasma ratio, and the *mdrla*(-/-) mice had a testes:plasma ratio of 2:1.

-15-

Example 3

The effect of P-glycoprotein inhibitors was investigated in *mdrla*(++) mice by pretreatment with equally divided doses given by intravenous tail vein injection, 30 minutes prior to and concurrently with administration of nelfinavir.

5      Inhibitors studied included the compound of formula (II) (2 x 0.5 to 25 mg/kg, Lilly Research Laboratories, Indianapolis, IN), verapamil (2 x 6.25 mg/kg, Sigma-Aldrich, St. Louis, MO) and quinidine (2 x 25 mg/kg, Sigma-Aldrich), each dissolved in 20% ethanol/0.9% saline; cyclosporine A (2 x 0.5 to 25 mg/kg, Novartis Pharma AG, Basel, Switzerland) dissolved in 10% ethanol/60% propylene glycol/30% water;

10     nelfinavir (2 x 25 mg/kg, Agouron Pharmaceuticals Inc., San Diego, CA), ritonavir (2 x 12.5 mg/kg Abbott Laboratories), saquinavir (2 x 25 mg/kg, Roche Products Ltd., Welwyn, UK), and indinavir (2 x 25 mg/kg, Merck Research Laboratories, West Point, PA) each dissolved in 10% ethanol/40% propylene glycol/50% 0.9% saline; and ketoconazole (2 x 25 mg/kg, Sigma-Aldrich) dissolved in 25% 0.2N HC1. All

15     drugs were injected in total volume of 4 µl/g and appropriate vehicle solutions were used in control studies.

Similar tissue distribution studies were also performed to study tissue distribution of [<sup>14</sup>C]-saquinavir (9.8 mCi/mmol, Roche Products Ltd) and [<sup>14</sup>C]-indinavir (8.5 mCi/mmol. Merck Research Laboratories), using the compound of formula (II) (2 x 25 mg/kg) as the P-glycoprotein inhibitor.

At least 3 mice were studied at each time point and differences in radioactivity between treated and control groups were analyzed by a two-sided Student's t-test with p < 0.05 as the limit of statistical significance.

As shown in Fig. 3, pretreatment with 25 mg/kg formula (II), 30

25     minutes prior to and concurrently with [<sup>14</sup>C]-nelfinavir, markedly altered the disposition of total radioactivity in *mdrla*(++) mice. The brain concentration-time profile in particular was especially affected, as seen in Fig. 2. In untreated mice, radioactivity in the brain was more than 17 times lower than that in plasma with a mean brain:plasma concentration ratio of 0.06, based on the relative area under the

30     concentration-time curves. Formula (II) increased brain levels by 20-fold in contrast to those in the plasma, which only changed 2-fold. As a result, formula (II) treatment produced an 10-fold increase in nelfinavir's brain:plasma distribution ratio.

-16-

Subsequent studies, also illustrated in Fig. 3, based on tissue distribution measured two hours after nelfinavir administration showed that these changes are dose-dependent. Moreover, 10- to 15-fold higher brain levels could be achieved without affecting nelfinavir plasma concentrations at total dosages between 12.5 mg and 25 mg/kg. Comparison of these findings with those in *mdrla*(-/-) mice indicated that if all of the effects of formula (II) are accounted for by P-glycoprotein inhibition, then the transporter is inhibited by about 75% following a total dose of 50 mg/kg formula (II). Similar results were obtained with nelfinavir levels in the testes, with P-glycoprotein activity being inhibited by over 90%. Similar findings were also noted after intravenous administration of [<sup>14</sup>C]-saquinavir, [<sup>14</sup>C]-indinavir and pretreatment with 50 mg/kg formula (II).

More modest, though statistically significant changes, were produced by cyclosporine A, ketoconazole, and ritonavir administration, but these largely reflected increased nelfinavir plasma concentrations rather than altered tissue distribution. Finally, neither quinidine, verapamil, nelfinavir, saquinavir, or indinavir produced significant changes in nelfinavir's disposition at the doses studied. The results are summarized in Table 1:

Table 1: Tissue levels of radioactivity (ng/g tissue) in wildtype and *mdrla*(-/-) mice at 2 hr after intravenous injection of [<sup>14</sup>C]-nelfinavir (5mg/kg). Mice were treated with varying doses of formula (II) or other known P-glycoprotein inhibitors, 50 mg/kg (unless otherwise noted) in two divided doses, given 30 min prior to and simultaneously with [<sup>14</sup>C]-nelfinavir. Data are shown as mean ± standard deviation.

	Plasma	Brain	Brain:Plasma Ratio	Testes	Testes:Plasma Ratio
<b>mdrla(+/+) Mice</b>					
Vehicle Control	98 ± 12	5.1 ± 1.9	0.06 ± 0.01	31 ± 5.8	0.29 ± 0.02
Ritonavir (25 mg/kg)	618 ± 112	22 ± 3.8	0.08 ± 0.05	59 ± 3.4	0.31 ± 0.14
Nelfinavir (50 mg/kg)	124 ± 11	7.9 ± 1.5	0.06 ± 0.02	47 ± 6.6	0.39 ± 0.07
Saquinavir (50 mg/kg)	117 ± 14	6.9 ± 1.9	0.06 ± 0.01	48 ± 11	0.43 ± 0.13
Indinavir (50 mg/kg)	100 ± 6.2	7.5 ± 0.9	0.08 ± 0.01	37 ± 8.1	0.39 ± 0.05
Vehicle Control	99 ± 6.7	9.4 ± 3.0	0.10 ± 0.02	41 ± 6.8	0.38 ± 0.06
Quinidine (50 mg/kg)	92 ± 2.5	5.1 ± 1.5	0.06 ± 0.01	47 ± 7.3	0.54 ± 0.06
Verapamil (12.5 mg)	91 ± 6.1	8.4 ± 2.1	0.09 ± 0.02	39 ± 3.0	0.44 ± 0.06

	Plasma	Brain	Brain:Plasma Ratio	Testes	Testes:Plasma Ratio	
Ketoconazole (50 mg/kg)	292 ± 68	57 ± 14	0.20 ± 0.02	87 ± 16	0.30 ± 0.04	
5	<b>Cyclosporine</b> Vehicle Control	103 ± 13	9.2 ± 1.2	0.10 ± 0.03	66 ± 12	0.42 ± 0.04
	1 mg/kg	120 ± 6.0	11 ± 2.4	0.10 ± 0.02	61 ± 7.0	0.51 ± 0.04
	4 mg/kg	322 ± 14	45 ± 20	0.13 ± 0.06	128 ± 10	0.40 ± 0.05
	12.5 mg/kg	698 ± 189	89 ± 19	0.18 ± 0.08	195 ± 54	0.30 ± 0.07
	25 mg/kg	659 ± 57	190 ± 43	0.30 ± 0.08	294 ± 50	0.44 ± 0.04
	50 mg/kg	954 ± 132	242 ± 46	0.27 ± 0.07	245 ± 55	0.25 ± 0.07
10	<b>Formula (II)</b> Vehicle Control	84 ± 4.9	6.6 ± 1.7	0.08 ± 0.02	47 ± 3.7	0.48 ± 0.07
	1 mg/kg	74 ± 14	9.4 ± 1.7	0.11 ± 0.04	56 ± 1.7	0.81 ± 0.13
	4 mg/kg	72 ± 4.8	24 ± 4.5	0.33 ± 0.04	95 ± 18	1.4 ± 0.33
	12.5 mg/kg	71 ± 11	60 ± 5.4	0.89 ± 0.16	108 ± 27	1.6 ± 0.44
	25 mg/kg	89 ± 8.1	89 ± 17	1.1 ± 0.28	168 ± 61	2.0 ± 0.48
	50 mg/kg	171 ± 12	243 ± 19	1.4 ± 0.08	187 ± 17	1.2 ± 0.19
15	<b>mdrla (-/-) Mice</b> Vehicle	89 ± 15	184 ± 20	2.3 ± 0.24	194 ± 34	2.1 ± 0.35
	Formula (II) (50mg/kg)	161 ± 24	318 ± 52	1.9 ± 0.12	207 ± 46	1.3 ± 0.13
20						

Although the invention has been described in detail with reference to preferred embodiments, variations and modifications exist within the scope and spirit of the invention as described and defined in the following claims.

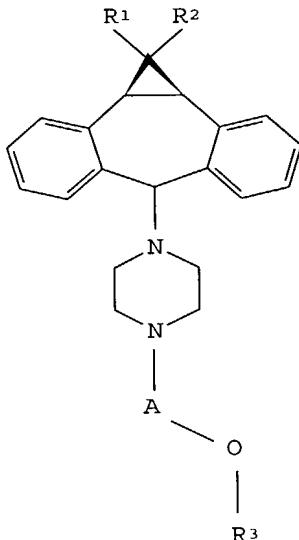
CLAIMS

1. A method for increasing the concentration of an HIV protease inhibitor in the brain of a patient, said method comprising administering to an HIV infected patient an amount of a 10,11-methanodibenzosuberane of formula (I):

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I

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wherein: A is  $-\text{CH}_2\text{CH}_2-$ ;  $-\text{CH}_2\text{CHR}^a\text{CH}_2-$  where  $\text{R}^a$  is H, OH or lower acyloxy; or  
 $-\text{CH}_2\text{CHR}^b\text{CHR}^c\text{CH}_2-$  where one of  $\text{R}^b$  or  $\text{R}^c$  is H, OH, or lower  
20 acyloxy, and the other is H;

$\text{R}^1$  is H, F, Cl, or Br;

$\text{R}^2$  is H, F, Cl, or Br; and

$\text{R}^3$  is heteroaryl or phenyl optionally substituted with F, Cl, Br,  $\text{CF}_3$ ,  
CN,  $\text{NO}_2$ , or  $\text{OCHF}_2$ ; or a pharmaceutically acceptable salt thereof; and

25 co-administering to the patient a therapeutically effective amount of  
the protease inhibitor.

2. The method of claim 1 wherein the patient is a male and the  
concentration of the HIV protease inhibitor is also increased in the patient's testes.

3. The method of claim 1 wherein the protease inhibitor is  
30 selected from the group of nelfinavir, indinavir, saquinavir, ritonavir, and amprenavir.

4. The method of claim 3 wherein the protease inhibitor is  
nelfinavir.

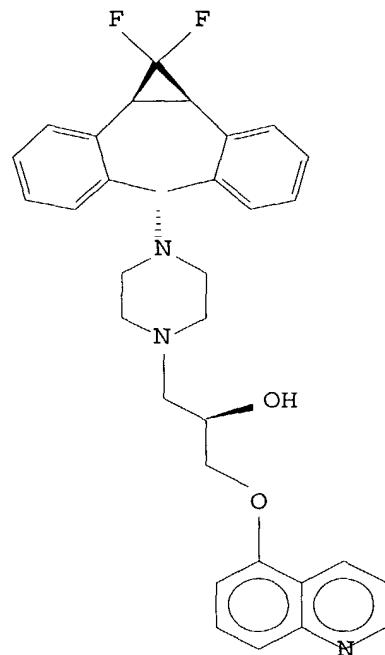
-19-

5. The method of claim 1 wherein R<sup>1</sup> and R<sup>2</sup> are F, A is -CH<sub>2</sub>CHR<sup>a</sup>CH<sub>2</sub>-, and R<sup>3</sup> is optionally substituted quinolyl.
6. The method of claim 5 wherein R<sup>a</sup> is OH and R<sup>3</sup> is quinol-5-yl.
7. The method of claim 1 wherein the methanodibenzosuberane of formula (I) is a compound of formula (II):

10

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II



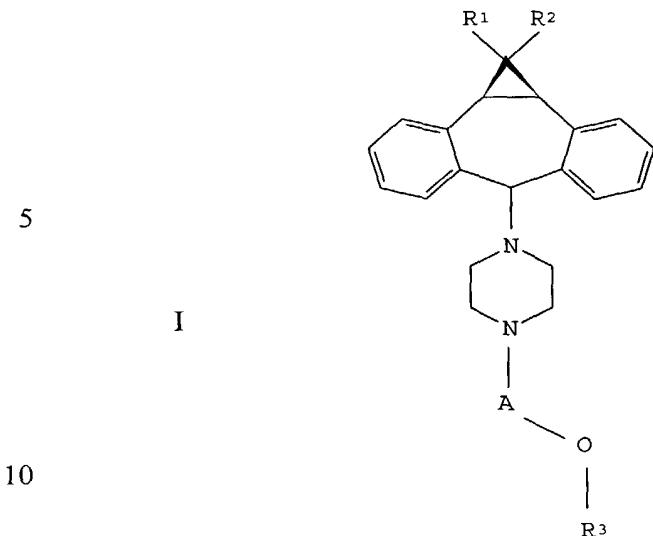
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8. A method of treating a patient having an HIV-1 infection comprising:

administering to the patient a therapeutically effective amount of a protease inhibitor, and

- co-administering to the patient an amount of a compound represented by formula (I):

30



wherein: A is  $-\text{CH}_2\text{CH}_2-$ ;  $-\text{CH}_2\text{CHR}^a\text{CH}_2-$  where  $\text{R}^a$  is H, OH or lower acyloxy; or  
 $-\text{CH}_2\text{CHR}^b\text{CHR}^c\text{CH}_2-$  where one of  $\text{R}^b$  or  $\text{R}^c$  is H, OH, or lower  
15 acyloxy, and the other is H;

$\text{R}^1$  is H, F, Cl, or Br;

$\text{R}^2$  is H, F, Cl, or Br; and

20  $\text{R}^3$  is heteroaryl or phenyl optionally substituted with F, Cl, Br,  $\text{CF}_3$ ,  
CN,  $\text{NO}_2$ , or  $\text{OCHF}_2$ ; or a pharmaceutically acceptable salt thereof;  
in an amount sufficient to increase brain levels of the protease inhibitor.

9. The method of claim 8 wherein  $\text{R}^1$  and  $\text{R}^2$  are F, A is  
 $-\text{CH}_2\text{CHR}^a\text{CH}_2-$ , and  $\text{R}^3$  is optionally substituted quinolyl.

10. The method of claim 9 wherein  $\text{R}^a$  is OH and  $\text{R}^3$  is  
quinol-5-yl.

25 11. The method of claim 8 wherein the amount of the compound of  
formula (I) is sufficient to increase the brain levels of the protease inhibitor without  
significantly increasing the concentration of the protease inhibitor in the patient's  
blood.

12. The method of claim 8, wherein the amount of the compound is  
30 also sufficient to increase concentrations of the protease inhibitor in the patient's  
testes.

-21-

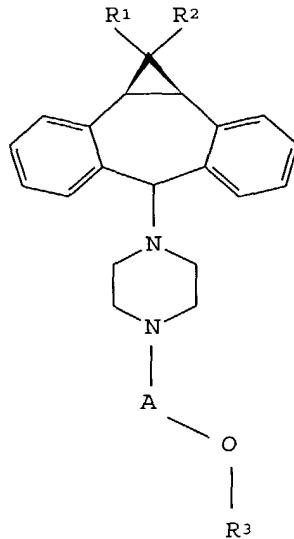
13. A pharmaceutical composition comprising  
an antiviral protease inhibitor;  
a 10,11-methanodibenzosuberane of formula (I):

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I



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wherein: A is -CH<sub>2</sub>CH<sub>2</sub>-; -CH<sub>2</sub>CHR<sup>a</sup>CH<sub>2</sub>- where R<sup>a</sup> is H, OH or lower acyloxy; or -CH<sub>2</sub>CHR<sup>b</sup>CHR<sup>c</sup>CH<sub>2</sub>- where one of R<sup>b</sup> or R<sup>c</sup> is H, OH, or lower acyloxy, and the other is H;

R<sup>1</sup> is H, F, Cl, or Br;

R<sup>2</sup> is H, F, Cl, or Br; and

R<sup>3</sup> is heteroaryl or phenyl optionally substituted with F, Cl, Br, CF<sub>3</sub>, CN, NO<sub>2</sub>, or OCHF<sub>2</sub>; or a pharmaceutically acceptable salt thereof; and a pharmaceutically acceptable carrier therefor.

14. The composition of claim 13 wherein the

methanodibenzosuberane of formula (I) is present in an amount effective to increase brain levels of the protease inhibitor.

15. The composition of claim 14 wherein the methanodibenzosuberane of formula (I) is present in an amount effective to increase brain levels of the protease inhibitor without significantly increasing plasma levels of the protease inhibitor.

16. The composition of claim 13 wherein the protease inhibitor is selected from the group consisting of nelfinavir, indinavir, saquinavir, ritonavir, or amprenavir.

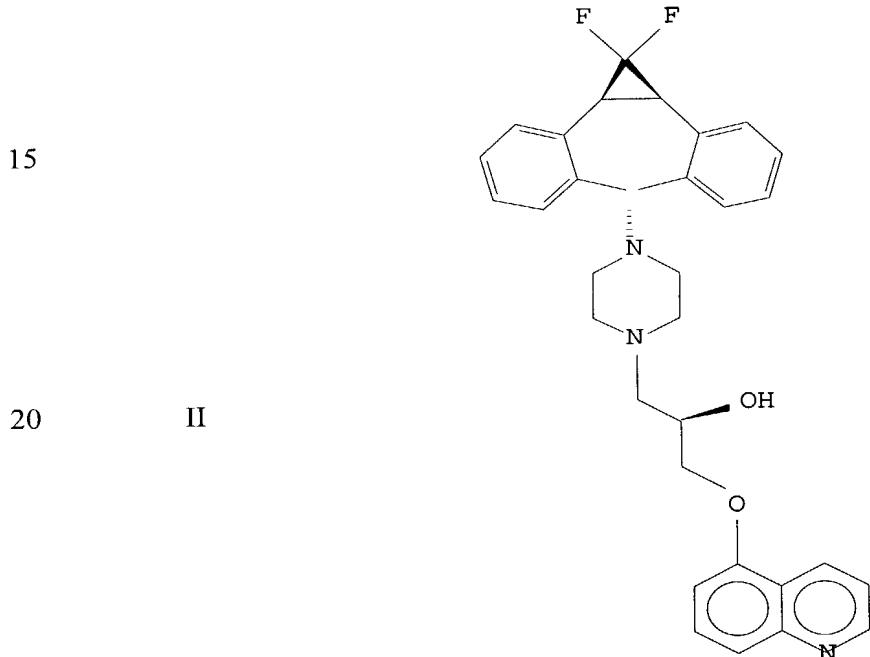
17. The composition of claim 16 wherein the protease inhibitor is  
5 nelfinavir.

18. The composition of claim 13 wherein R<sup>1</sup> and R<sup>2</sup> are F.

19. The composition of claim 13 wherein A is -CH<sub>2</sub>CHR<sup>a</sup>CH<sub>2</sub>-.

20. The composition of claim 13 wherein R3 is a optionally substituted quinolyl.

10 21. The composition of claim 13 wherein the 10,11-methanodibenzosuberane is the compound of formula (II):



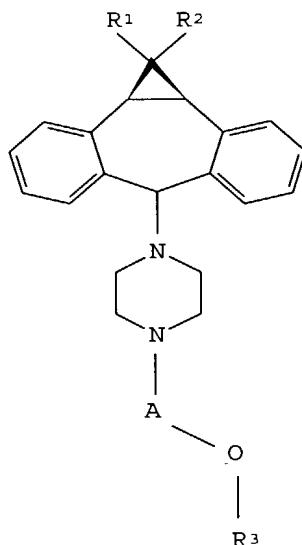
22. The composition of claim 13 wherein the methanodibenzosuberane comprises about 0.005 to 95% of the composition.

## 23. Use of a 10,11-methanodibenzosuberane of formula (I):

5

I

10



wherein: A is  $-\text{CH}_2\text{CH}_2-$ ;  $-\text{CH}_2\text{CHR}^a\text{CH}_2-$  where  $\text{R}^a$  is H, OH or lower acyloxy; or  
 15  $-\text{CH}_2\text{CHR}^b\text{CHR}^c\text{CH}_2-$  where one of  $\text{R}^b$  or  $\text{R}^c$  is H, OH, or lower  
 acyloxy, and the other is H;

$\text{R}^1$  is H, F, Cl, or Br;

$\text{R}^2$  is H, F, Cl, or Br; and

$\text{R}^3$  is heteroaryl or phenyl optionally substituted with F, Cl, Br,  $\text{CF}_3$ ,

20 CN,  $\text{NO}_2$ , or  $\text{OCHF}_2$ ; or a pharmaceutically acceptable salt thereof;

for the manufacture of a medicament for the treatment of HIV in a patient undergoing treatment with an HIV protease inhibitor.

24. The use of claim 23 for increasing the concentration of the protease inhibitor in the brain of a patient undergoing treatment with an HIV protease inhibitor.

25. The use of claim 24 for increasing the concentration of the protease inhibitor in the patient's testes.

26. The use of any one of claims 23-25 for the manufacture of a medicament wherein the protease inhibitor is selected from the group of nelfinavir, 30 indinavir, saquinavir, ritonavir, and amprenavir.

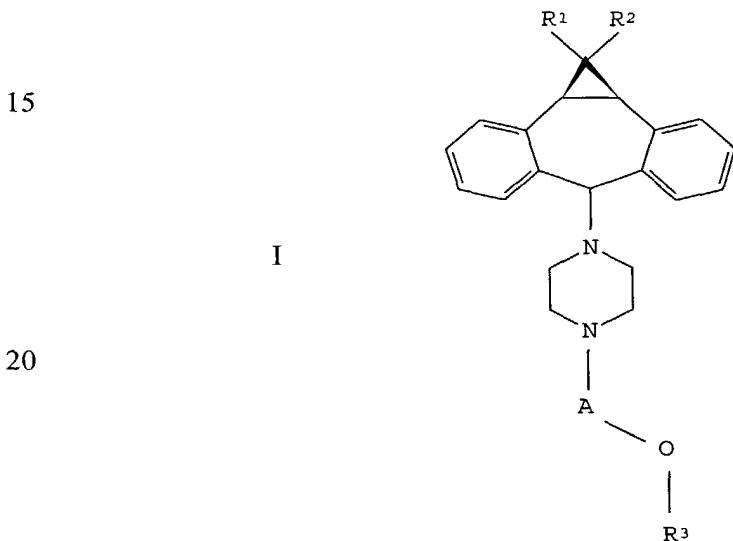
-24-

27. The use of any one of claims 23-26 for the manufacture of a medicament wherein R<sup>1</sup> and R<sup>2</sup> are F, A is -CH<sub>2</sub>CHR<sup>a</sup>CH<sub>2</sub>-, and R<sup>3</sup> is optionally substituted quinolyl.

28. The use of claim 27 for the manufacture of a medicament  
5 wherein R<sup>a</sup> is OH and R<sup>3</sup> is quinol-5-yl.

29. The use of claim 23 for the manufacture of a medicament for increasing brain levels of the protease inhibitor without significantly increasing plasma levels of the protease inhibitor.

30. Use of an HIV protease inhibitor for the manufacture of a  
10 medicament for the treatment of HIV wherein the concentration of HIV protease inhibitor in the brain is increased by co-administration with a 10,11-methanodibenzosuberane of formula (I):



wherein: A is -CH<sub>2</sub>CH<sub>2</sub>-; -CH<sub>2</sub>CHR<sup>a</sup>CH<sub>2</sub>- where R<sup>a</sup> is H, OH or lower acyloxy; or -CH<sub>2</sub>CHR<sup>b</sup>CHR<sup>c</sup>CH<sub>2</sub>- where one of R<sup>b</sup> or R<sup>c</sup> is H, OH, or lower acyloxy, and the other is H;

R<sup>1</sup> is H, F, Cl, or Br;

R<sup>2</sup> is H, F, Cl, or Br; and

30 R<sup>3</sup> is heteroaryl or phenyl optionally substituted with F, Cl, Br, CF<sub>3</sub>, CN, NO<sub>2</sub>, or OCHF<sub>2</sub>; or a pharmaceutically acceptable salt thereof.

-25-

31. The use of claim 30 wherein the concentration of the protease inhibitor in the patient's testes is also increased.

32. The use of any one of claims 30-31 wherein the protease inhibitor is selected from the group of nelfinavir, indinavir, saquinavir, ritonavir, and  
5 amprenavir.

33. The use of claim 30 wherein the protease inhibitor is nelfinavir.

34. The use of any one of claims 30-33 wherein R<sup>1</sup> and R<sup>2</sup> are F,  
A is -CH<sub>2</sub>CHR<sup>a</sup>CH<sub>2</sub>-, and R<sup>3</sup> is optionally substituted quinolyl.

35. The use of claim 34 wherein R<sup>a</sup> is OH and R<sup>3</sup> is quinol-5-yl.

10 36. The use of claim 30 wherein the brain levels of the protease inhibitor are increased without significantly increasing plasma levels of the protease inhibitor.

ANTIVIRAL THERAPY USE OF P-GLYCOPROTEIN MODULATORSAbstract of the Disclosure

5                 The present invention relates to a pharmaceutical composition comprising a 10, 11 methanodibenzosuberane and use thereof for the treatment of HIV infection. Co-administration of the 10, 11 methanodibenzosuberane with an HIV protease inhibitor increases the concentration of the protease inhibitor in certain tissues, including the brain and testes, without substantially increasing plasma levels  
10                 of the protease inhibitor. Accordingly, additional antiviral therapy can be achieved without use of increased drug dosages, thereby reducing the potential for occurrence of undesirable side effects deriving from drug toxicity.

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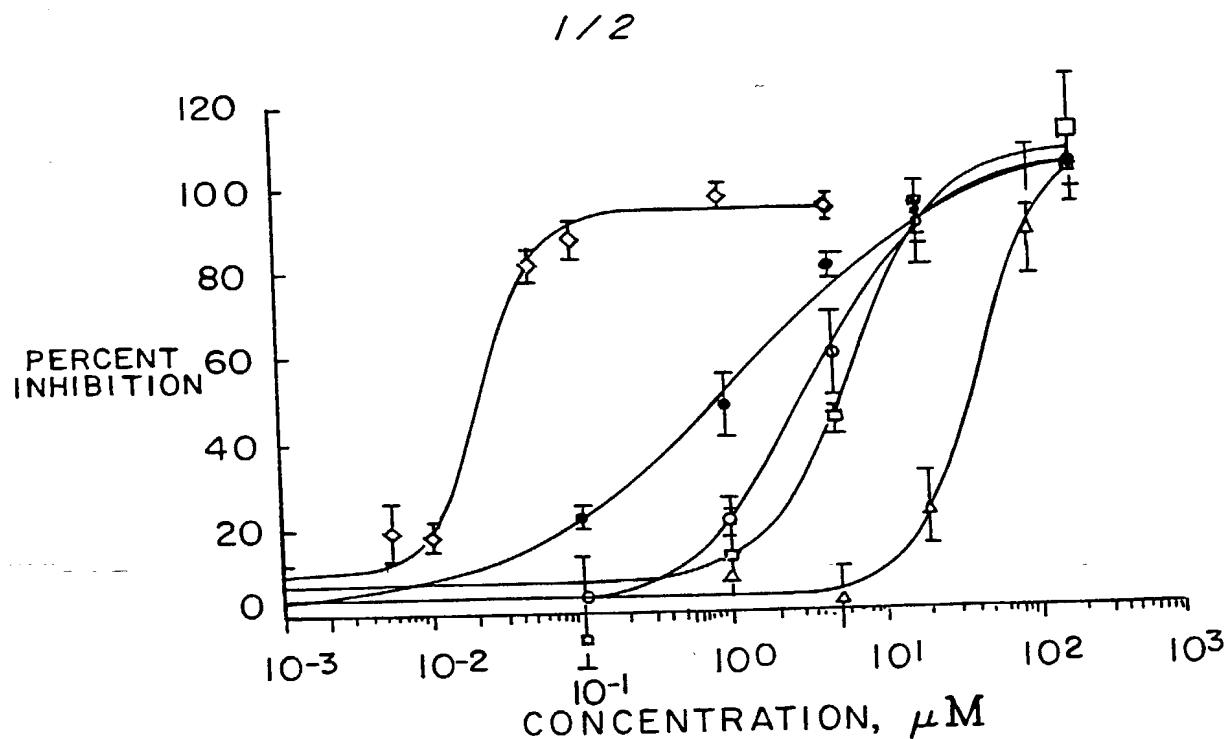


FIG. 1

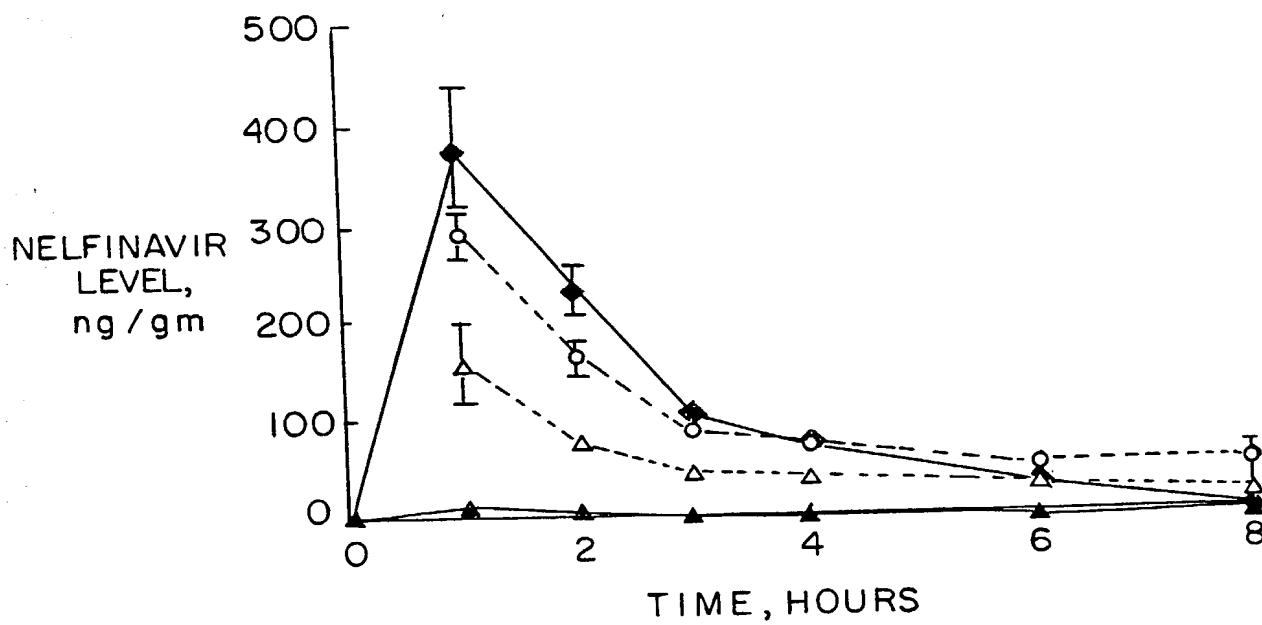
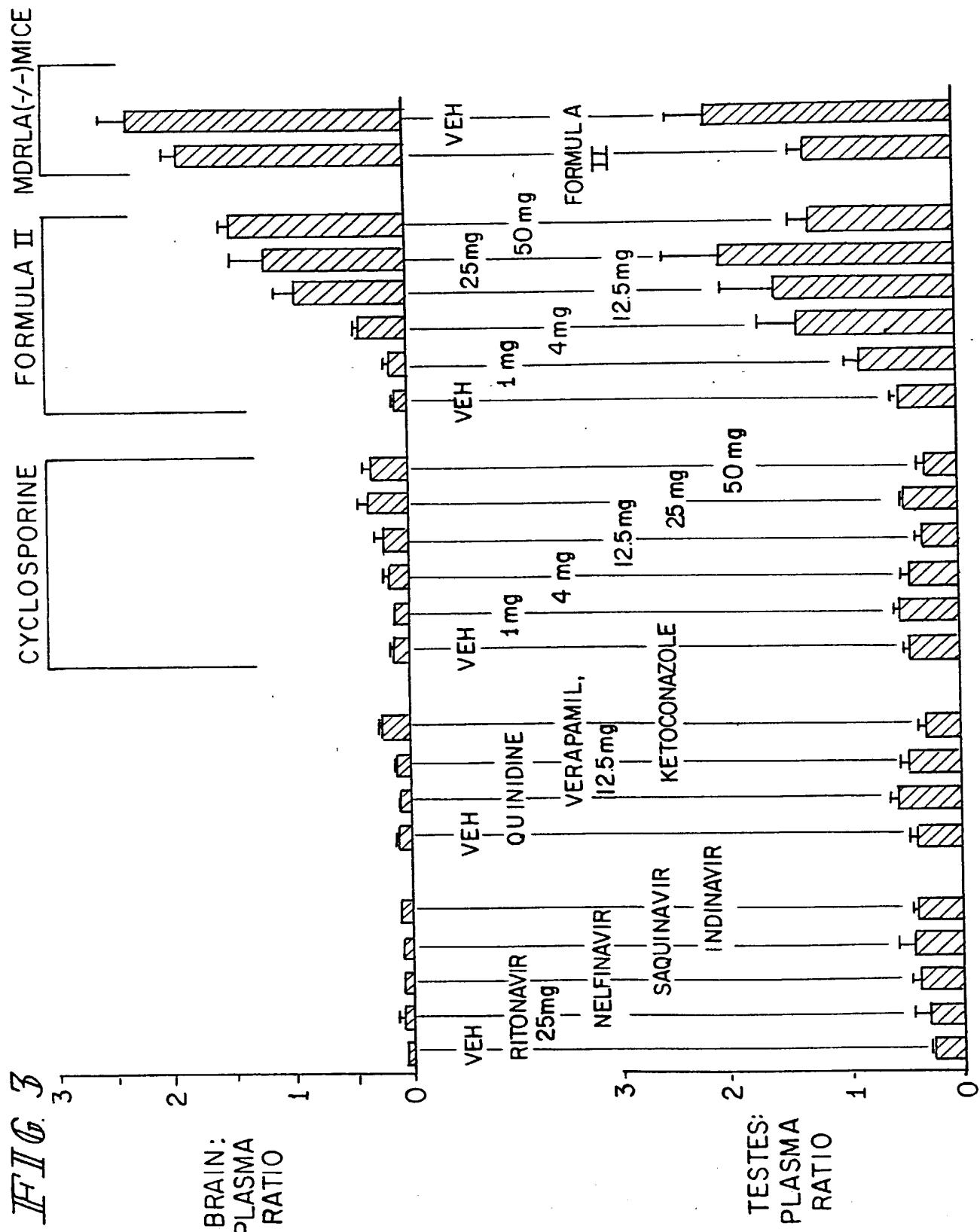


FIG. 2

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2/2



Attorney Docket No.: 3051-**DECLARATION AND POWER OF ATTORNEY -- PATENT APPLICATION**

As a below named inventor, I hereby declare that I believe I am the original, first and sole inventor (*if only one name is listed below*) or an original, first and joint inventor (*if plural names are listed below*) of the subject matter which is claimed and for which a patent is sought in the application entitled:

**ANTIVIRAL THERAPY USE OF P-GLYCOPROTEIN MODULATORS**

specification of which

(check one)

is attached hereto

XX was filed on 07 August 2000 (07.08.00)

as

United States Application Serial No.

or

PCT International Application No. PCT/US00/

and was amended on

(if applicable)

I hereby declare that I have reviewed and understand the contents of the above-identified specification, including the claims, as amended by any amendment referred to herein.

I acknowledge the duty to disclose information which is material to patentability as defined in Title 37, Code of Federal Regulations, §1.56.

I hereby claim foreign priority benefits under Title 35, United States Code, §119(a)-(d) of any foreign application(s) for patent or inventor's certificate on which priority is claimed (as listed below) and I have also identified below any foreign application for patent or inventor's certificate having a filing date before that of the application on which priority is claimed:

## Prior Foreign Application(s)

## Priority Claimed

(Number)	(Country)	(Day/Month/Year Filed)	Yes	No
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(Number)	(Country)	(Day/Month/Year Filed)	Yes	No
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I hereby claim benefit under Title 35, United States Code, § 119(e) of any United States provisional application(s) listed below.

09/370,26609 August 1999 (09.08.99)

Application Number

Filing Date **(Converted to Provisional per  
Decision Dated 03 July 2000)**

Application Number

Filing Date

I hereby claim the benefit under Title 35, United States Code, §120 of any United States application(s) listed below and, insofar as the subject matter of each of the claims of this application is not disclosed in the prior United States application in the manner provided by the first paragraph of Title 35, United States Code, §112, I acknowledge the duty to disclose material information as defined in Title 37, Code of Federal Regulations, §1.56(b) which occurred between the filing date of the prior application and the national or PCT international filing date of this application:

Application Serial No.	Filing Date	Status-patented, pending, abandoned
------------------------	-------------	-------------------------------------

Application Serial No.	Filing Date	Status-patented, pending, abandoned
------------------------	-------------	-------------------------------------

I hereby appoint William R. Coffey, Reg. No.24023; Richard D. Conard, Reg. No.27321; Steven R. Lammert, Reg. No. 27653; Richard A. Rezek, Reg. No. 30796; Nancy J. Harrison, Reg. No. 27083; Dilip A. Kulkarni, Reg. No. 27510; David B. Quick, Reg. No. 31993; Jill T. Powlick, Reg. No. 42088; Arland T. Stein, Reg. No. 25062; William B. Richards, Reg. No. 44301; Christopher E. Haigh, Reg. No. 46377; James R. Sweeney II, Reg. No. 45670; Perry Palan, Reg. No. 26213; Mark M. Newman, Reg. No. 31472; Bobby B. Gillenwater, Reg. No. 31105; Paul B. Hunt, Reg. No. 37154; Michael S. Gzybowski, Reg. No. 32816; Alice O. Martin, Reg. No. 35604; and Gregory S. Cooper, Reg. No. 40965, as attorneys of record with full power of substitution and

revocation to prosecute this application, and to transact all business in the Patent and Trademark Office connected therewith, and I specify that communications regarding the application be directed to:

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Indianapolis, Indiana 46204  
Telephone (317) 236-1313

I hereby declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code, and that such willful false statements may jeopardize the validity of the application or any patent issued thereon.

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Country of Citizenship

08/29/00

Date

Canada (CA)

Country of Citizenship

08/29/2000

Date

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Country of Citizenship

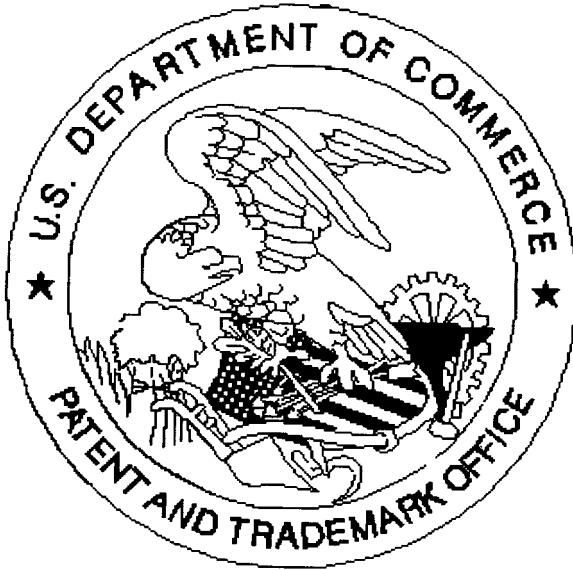
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